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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/601,645	DAHM ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,22-24,26-38,52-61,63-67,69-71,73-78 and 85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,22-24,26-38,52-61,63-67,69-71,73-78 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 8, 2003. Currently, claims 1-19, 22-24, 26-38, 52-61, 63-67, 69-71, 73-78, 85 are pending.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims and applicant's arguments.

3. This action contains new grounds of rejection following an updated search.

4. The arguments have been thoroughly considered and are moot in view of the new grounds of rejection.

New Grounds of Rejection
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Newly amended Claims 1, 2, 4, 7-11, 14-19, 22-24, 26-28, 34-38, 52-56, 60-61, 63-64, 67, 69-71, 73, 75-78, 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Cech et al (US Pat. 6,166,178, December 26, 2000, filed November 19, 1997) in view of Van Vlasselaer et al (US Pat. 5,648,223, July 1997) and further in view of Bosslet et al. (Br. J. Cancer, Vol. 44, pages 356-362, 1981).

It is noted that only the specification for the patent has been provided because the sequences are not relied upon in the rejection and are very extensive in length.

Cech et al. (herein referred to as Cech) teaches methods of quantitating tumor cells in a body fluid by concentrating tumor cells in a sample of body fluid, amplifying mRNA coding for the catalytic subunit of telomerase and quantitatively determining the amount of amplified nucleic acid. Specifically, Cech teaches methods of diagnosing cancer in a patient by obtaining a biological sample from the patient and detecting a hTRT gene product in the patient sample, where the detection of the hTRT gene product in the sample is correlated with a diagnosis of cancer (col. 6, lines 20-40). Cech also teaches that the determination of an hTRT gene, mRNA or protein level above normal or standard range is indicative of the presence of telomerase-positive cells, or immortal of which certain tumor cells are examples (col. 99, lines 5-20). Cech specifically teaches that hTRt gene or gene product (i.e., mRNA or polypeptide) is preferably detected and/or quantified in a biological sample (col. 104, lines 59-65). Cech teaches that biological samples include blood, blood cells, body fluids, e.g., urine, sputum, amniotic fluid, blood, peritoneal fluid, pleural fluid, semen (col. 104, lines 65-68)(limitations of Claim 11, 24-28). Cech teaches that cells or tissues may be

fractionated before analysis, for example by a cell sorter may be used to sort cells according to characteristics such as expression of a surface antigen (col. 105, lines 10-12). Cech teaches that nucleic acids may be isolated from the cell by any separation of the species or target to be detected from any other substance in the mixture (col. 105, lines 55-65)(limitations of Claim 4). Cech teaches that the assay for detection of hTRT are amplification based to amplify all or part of an hTRT gene or transcript where the amplification product is then detected directly or indirectly (col. 106, lines 45-55). Cech teaches primers useful for PCR amplification of hTRT are provided in Table 2 (col. 107, lines 1-5). Cech teaches that amplified products may be directly analyzed by size (gel electrophoresis); by hybridization to a target nucleic acid immobilized on a solid support; by sequencing; by detection of a fluorescent, phosphorescent, or radioactive signal (col. 108, lines 1-5)(limitations of Claim 8-9). Cech teaches that in one possible embodiment PCR amplification is carried out in a 50ul solution containing the nucleic acid sample (e.g., cDNA obtained through reverse transcription of hTRT RNA), dNTP, hTRT specific PCR primers, Taq polymerase, PCR buffer (col. 107, lines 12-25)(limitations of Claim 2, 14, 15). Cech teaches that quantification methods may include the co-amplification reactions to allow for normalization of the cell number in a sample as compared to the amount of hTRT in the sample (col. 108, lines 45-65)(limitations of Claim 7, 10).

Cech does not specifically teach enrichment by centrifugation to collect tumor cells.

However, Van Vlasselaer teaches methods for enriching tumor cells prior to analyzing. Percoll and Ficoll were routinely used in the art as cell separation media

(col. 4, lines 60- col. 5, lines 5)(limitations of claim 23). Van Vlassalaer teaches that the medium density is adjusted to the density of the cell type (col. 9, lines 47-66, col. 14, Example 6.1.1 and 6.1.2)(limitations of Claim 21, 22, 24 and 62-64). Van Vlassalaer teaches that a large volume of complete blood may be directly placed on the density gradient. Peripheral blood may be collected in anti-coagulant containing tubes (col. 4, lines 37-40)(limitations of Claim 24-27). Van Vlassalaer teaches that for breast tumor cells, the specific density was adjusted within 0.0005 g/ml of the specific density of the tumor cells and the centrifugation speed is at a gravitational force sufficient to pellet the cells (col. 16, lines 61-67). Additionally, Van Vlasselaer teaches methods that may cause cells to be heavier than their normal density so that they are pelleted during centrifugation, namely linking a heavy particle such as a binding agent to selected cells. Van Vlassalaer teaches that centrifugation is carried out in a tube divided by a barrier wherein the barrier is an annular ring (col. 5, lines 30-54).

Bosslet also teaches a method of separating tumor cells from the gradients to analyze the viable tumor cells in vitro. Bosslet teaches that in linear Percoll density gradients, tumor cells were found in bands ranging from 1.051 to 1.068 g/ml whereas normal SL were found in bands ranging from 1.075-1.082 (page 357, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Cech with the enrichment method of Van Vlasselaer with the range from 1.060-1.067 g/ml as taught by Bosslet prior to molecular analysis. Van Vlasselaer teaches that after centrifugation is performed and cells are collected, tumor cell may be screened by molecular means (col. 4 lines 20-22). Bosslet teaches

that in linear Percoll density gradients, tumor cells were found in bands ranging from 1.051 to 1.068 g/ml whereas normal SL were found in bands ranging from 1.075-1.082 (page 357, col. 2). Therefore, the ordinary artisan would have been motivated to have performed the rapid and high yield isolation or enrichment of tumor cells in the range of from 1.060-1.067 g/ml prior to analysis by the method of Cech for the increased sensitivity and efficiency. The numerous means of enrichment and isolation of Van Vlasselaer would be obvious means to enriching cells in a blood sample. The final step of Claim 1 is directed to correlating the amount of amplified nucleic acid with the number of tumor cells in the body fluid. As asserted in the response filed September 8, 2003, "the correlation between the amount of amplified mRNA encoding a gene and the number of cells expressing that gene was routine and well-known to those of skill in the art at the earliest priority date of the instant application." Thus, as particularly pointed out by the response the correlation of the amount of amplified nucleic acid detected by Cech and the number of tumor cells was well known and routine to those of skill in the art. Therefore, the skilled artisan would have been motivated to determine the number of the cells present in the sample using the well known and routine methods to enable quantification. Therefore, it would have been obvious to the ordinary artisan to employ a cell separation medium that was proven in the art and readily available.

With regard to Claims 22, 24, 62-64, it would have been obvious to the ordinary artisan to adjust the density of the cell separation medium and centrifugation speed according to the type of tumor cell to be concentrated. It would have been obvious to

provide a substance that prevents platelets from sticking to the tumor cells and to remove the platelets as routinely practiced in the art.

With respect to Claim 71, the ordinary artisan would have necessarily isolated telomerase-positive non-tumor cells from tumor cells my generically separated tumor cells from normal cells, as taught in Bosslet.

The examiner recognizes that the instant specification has identified the range from 1.060-1.067 g/ml as a particularly good separation medium of a density range (page 17). The specification exemplifies subjecting the blood mixture to a density of 1.065 g/ml (page 30). It is clear from the art and the specification that the critical limit to the range is the 1.067 upper limit because normal cells are found in bands nearing the upper limit. Thus, the upper limit of the range appears to be the critical aspect of the invention. The closest prior art, Bosslet teaches that tumor cells could be isolated at density gradients with densities up to 1.068 g/ml. In determining unexpected results, the MPEP requires that the closest prior art be compared to the claimed invention (see MPEP 716.02(e). In the current case, the specification performs the analysis of the density gradients at 1.065 and 1.070. The specification determines that separation of cells at a density of 1.070 yields a sufficiently high number of telomerase-active leukocytes in the interphase (page 32 of the specification). In the event that the applicant compares the closest prior art of Bosslet to the data shown in the specification, namely the range of up to 1.068 taught by Bosslet relative to the claimed range of 1.060 to 1.067, a significant difference due to the reduction in density from 1.068 to 1.067 might demonstrate a secondary consideration relating to the importance

and criticality of the range. However, currently, the art of Bosslet teaches an upper limit of 1.068 g/ml for separation, whereas the claims are directed to 1.067. This difference does not appear to be unexpected, as the ranges of Bosslet and the claims share significant overlap. Therefore, the evidence currently of record does not yield an unexpected result which serves as a secondary consideration to overcome the prima facie case.

Response to Arguments

The response traverses the rejection. The response asserts that all of the claims include one element, namely the method for the quantification of tumor cells in a body fluid. The response argues that neither of the cited references teaches or suggests a method for the quantification of tumor cells in a body fluid. This argument has been reviewed but is not convincing because Cech teaches quantifying the amount of amplified nucleic acid. The response argues that Cech does not teach or suggest correlating the amount of the amplified mRNA to the number of tumor cells in the sample. Throughout the response the applicant states, "such correlation is routine, since one of skill in the art could determine the amount of mRNA by comparison with a standard" (page 11 of the response filed September 8, 2003). Additionally, "the correlation between the amount of amplified mRNA encoding a gene and the number of cells expressing that gene was routine and well-known to those of skill in the art at the earliest priority date of the instant application" (page 17 of the response filed September 8, 2003).

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Cech et al (US Pat. 6,166,178, December 26, 2000, filed November 19, 1997) in view of Van Vlasselaer et al (US Pat. 5,648,223, July 1997) and Bosslet et al. (Br. J. Cancer, Vol. 44, pages 356-362, 1981) above in view of Gwynn et al. (US Pat. 6,025,156, February 2000).

Neither Cech, Vlasselaer nor Bosslet specifically teaches using DNAase for removal of DNA from a sample.

However, Gwynn et al. (herein referred to as Gwynn) teaches using DNAase for removal of DNA from RNA samples. Once the DNAase was added and DNA was removed, RNA was pelleted and reverse transcribed into cDNA (col. 31, lines 50-65).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of generating cDNA of Cech with the teachings of Gwynn. Gwynn teaches addition of DNAase facilities the removal of DNA from the sample such that RNA may be obtained. Therefore, the ordinary artisan would have realized that in order to remove DNA from RNA samples so that the RNA may be in turn transcribed, DNAase may be added.

8. Claims 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Cech et al (US Pat. 6,166,178, December 26, 2000, filed November 19, 1997) in view of

Van Vlasselaer et al (US Pat. 5,648,223, July 1997) and Bosslet et al. (Br. J. Cancer, Vol. 44, pages 356-362, 1981) above in view of Shelby (GB 2 260 811, April 1993).

Neither Cech, Vlasselaer nor Bosslet specifically teaches a method of centrifugation by the allowing of the sample to cool following centrifugation.

However, Shelby teaches that diagnosis or monitoring of cancer or a malignant tumor may be effected by the detection of mRNA in a sample such as peripheral blood where the cells are not normally present and testing the sample (abstract). The detection technique of Shelby involves extracting the total cellular mRNA in a sample using reverse transcriptase to prepare cDNA, then carrying out PCR with appropriate primers so as to selectively amplify the cDNA (abstract). Shelby teaches cooling after centrifugation was routinely practice in the art (page 10, last paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of centrifugation by the allowing of the sample to cool following centrifugation.

9. Claims 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Cech et al (US Pat. 6,166,178, December 26, 2000, filed November 19, 1997) in view of Van Vlasselaer et al (US Pat. 5,648,223, July 1997) and Bosslet et al. (Br. J. Cancer, Vol. 44, pages 356-362, 1981) above in view of Gelmini et al. (Clinical Chemistry, Vol. 43, No. 5, pages 752-758, 1997).

Neither Cech, Vlasselaer nor Bosslet specifically teaches the continuous monitoring of PCR reaction.

However, Gelmini teaches methods of quantitative polymerase chain reaction which is quantitative, accurate, and time-saving. The method of Gelmini uses fluorogeneic probes to assess amplification. Gelmini teaches that during PCR cycling, the probe specifically hybridizes to the corresponding template and then is cleaved and results in increase of fluorescence emission of the reporter dye. The increased of fluorescence is proportional to the amount of the specific PCR product (page 753, col. 2). Gelmini teaches that the fluorescence was measured with a luminescence spectrometer (page 754, col. 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Cech for amplification with the method of Gelmini for the real time quantitative PCR. The ordinary artisan would have been motivated to have applied the method of Gelmini because Gelmini teaches the TaqMan PCR assay gave accurate, quantitative results.

10. Claims 13, 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Cech et al (US Pat. 6,166,178, December 26, 2000, filed November 19, 1997) in view of Van Vlasselaer et al (US Pat. 5,648,223, July 1997) and Bosslet et al. (Br. J. Cancer, Vol. 44, pages 356-362, 1981).

Neither Cech, Vlasselaer nor Bosslet specifically teaches SEQ ID NO: 1 and 2 however, Cech teaches numerous primers suitable for PCR amplification of hTRT.

The nucleic acid sequences of SEQ ID NO: 1 and 2 are functional equivalents to the primers taught by Cech. The ordinary artisan would have recognized that primer designed to amplify all or part of an hTRT gene may be used. Cech teaches the

parameters needed to design appropriate primers for hTRT. For example, Cech teaches that the primers are sufficiently complementary to the hTRT gene. The primers are typically at least 6 bases in length, typically between about 12 and about 50 bases (col. 106, lines 45-68). Cech teaches that one of skill in the art having the disclosure will be able, using routine methods will select primer to amplify all or any portion of hTRT gene. Therefore, SEQ ID NO: 1 and 2 of the instant application were merely selected by the routine methods provided by Cech for the amplification of all or part of the hTRT nucleic acid.

11. Claims 12, 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Cech et al (US Pat. 6,166,178, December 26, 2000, filed November 19, 1997) in view of Van Vlasselaer et al (US Pat. 5,648,223, July 1997) and Bosslet et al. (Br. J. Cancer, Vol. 44, pages 356-362, 1981) above in view of Melvin et al. (WO 97/12246, April 1997).

Neither Cech, Vlasselaer nor Bosslet specifically teaches using controls.

However, Melvin et al. (herein referred to as Melvin) teaches that in RT-PCR experiments B-actin was used as a positive control. Melvin teaches that the negative control was sterile water in place of cDNA (page 17).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Cech to include controls as taught by Melvin. Controls are essential in each scientific experiment to ensure that the results obtained

are due to the experiment and not due to external factors. Therefore, the ordinary artisan would be motivated to have used controls in the study of Cech.

12. Claims 30-33, 65-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Cech et al (US Pat. 6,166,178, December 26, 2000, filed November 19, 1997) in view of Van Vlasselaer et al (US Pat. 5,648,223, July 1997) and Bosslet et al. (Br. J. Cancer, Vol. 44, pages 356-362, 1981) and further in view of Oka et al (US Pat. 5,298,165, March 1994).

Neither Cech nor Van Vlasselaer nor Bosslet specifically teach centrifugation with filters of porous barriers which have certain properties.

However Oka et al. (herein referred to as Oka) teaches that filtration of blood may be effected with different membranes, filters or porous barriers. Oka teaches that the average pore size of one of the filters is preferably from 4 to 25 um (col. 10, lines 40-45). Additionally, Oka teaches numerous different filters with different thickness including thickness of 2 mm, 5 mm.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Cech in view of Van Vlasselaer to enrich using a porous barrier, filter or sieve as taught by Oka for the express benefit of enriching or isolating cells. The filters of Oka are representative of filters taught in the art. As exemplified by Oka the specific specifications of the filter are dependent upon the material wishing to be isolated. Therefore, with regard to the pore size and thickness of filters, these are routinely optimizable based upon the desired parameters, since Oka

teaches how densities may be determined the optimization of the workable pore size and thickness is not inventive. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Conclusion

13. No claims allowable over the art.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
November 6, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER